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Impact of oral vitamin C on histamine levels and seasickness

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Abstract.
BACKGROUND: Seasickness is a risk aboard a ship. Histamine is postulated as a causative agent, inversely related to the intake of vitamin C. Persons with mastocytosis experienced improvement of nausea after the intake of vitamin C.
OBJECTIVE: To determine whether vitamin C suppresses nausea in 70 volunteers who spent 20 minutes in a life raft, exposed to one-meter-high waves in an indoor pool.
METHOD: Double-blind placebo-controlled crossover study. Two grams of vitamin C or placebo was taken one hour before exposure. Blood samples were taken one hour before and after exposure to determine histamine, diamine oxidase, tryptase, and vitamin C levels.
Symptom scores were noted on a visual analog scale. On the second day the test persons were asked which day they had felt better.
RESULTS: Seven persons without symptoms were excluded from the analysis. Test persons had less severe symptoms after the intake of vitamin C ($p < 0.01$). Scores on the visual analog scale were in favor of vitamin C, but the difference was not significant.
Twenty-three of 63 persons wished to leave the raft earlier: 17 after the intake of placebo and 6 after the intake of vitamin C ($p < 0.03$). Women ($p < 0.02$) and men below 27 years of age ($p < 0.02$) had less pronounced symptoms after the intake of vitamin C. Histamine ($p < 0.01$) and DAO levels were increased after the intake of vitamin C ($p < 0.001$) and after placebo (n.s.). The fact that the second test day was rated less stressful by most volunteers is indicative of habituation.
CONCLUSIONS: Some of the data show that vitamin C is effective in suppressing symptoms of seasickness, particularly in women and men younger than 27 years of age, and is devoid of side effects. Histamine levels were initially increased after the test persons had been exposed to waves.

Keywords: Seasickness, histamine, diamine oxidase, vitamin C, German Navy

1. Introduction

Approximately 80% of persons traveling on sea experience seasickness. It constitutes a risk for the health and safety of the crew as well as the ship. No other condition leads as rapidly to thoughts of suicide. A proverb

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sums up this pathetic condition quite aptly: One first fears one will die, then fears one will not.

Seasickness is caused by a miscommunication between the vestibular, visual and somatosensory system [2]. Nausea and vomiting are the predominant symptoms.

Seasickness is primarily triggered by elevated histamine levels in the brain [21]. Drugs like scopolamine (muscarinic receptors), amphetamine (various adrenergic and noradrenergic receptors) and phenytoin (its site of action is unclear, but it is a highly effective anti-motion-sickness drug) are effective in counteracting this condition. Therefore, these add-on mechanisms must also be taken into account.

The majority of drugs used to treat seasickness are antihistamines. In animal models it was found that the blockade of histidine decarboxylase (degrades histidine to histamine) prevents seasickness [14,21]. On the other hand, an inverse relation was registered between vitamin C and histamine [1,9]. If this were true, a model of Nature such as mastocytosis with elevated histamine levels should be associated with reduced vitamin C levels. In fact, we registered significantly lower levels of vitamin C in patients with mastocytosis [8]. In addition, persons with nausea ceased to experience nausea after the intake of vitamin C [8].

We aimed to investigate whether vitamin C would suppress nausea in persons exposed to motion at sea. In cooperation with the German Navy, volunteers in an inflatable life raft were exposed to artificial waves in a large indoor swimming pool.

2. Material and methods

After approval by the ethics committee (University of Kiel, AZ 56/05 (II), EUDRA-CT no. 2005-00221124) and written informed consent of the participants, 70 volunteers (20 women and 50 men aged 19 to 60 years, mean age 31 ± 11 years, median 27 years) were included in a double-blind placebo-controlled crossover study. The participants were exposed to waves on two separate days. The volunteers were randomized into two groups of equal size: group VP received vitamin C before exposure on the first day and placebo before exposure on the second day, whereas the sequence was reversed in group PV. The exposure took place in a large indoor swimming pool for divers of the Germany Navy. The test persons spent 20 minutes in an inflatable life raft. They were asked to avoid alcoholic beverages and histamine-rich food the previous day and during breakfast the next day.

No woman had her menstruation on the days of testing; seasickness is known to be more common during menstruation [7]. Women are also known to be less susceptible to seasickness at the day of ovulation and when taking contraceptive pills [16].

Inflatable life raft exposed to 1-meter-high waves.

Blood samples were taken one hour prior to the test in order to determine histamine, diamine oxidase (DAO, a histamine-degrading enzyme), tryptase, and vitamin C levels.

Each person took 4 vitamin C tablets (500 mg) or placebo one hour before the test. One half of the participants were randomized to vitamin C and then placebo, while the other half were treated in reverse sequence. The test persons were asked to keep the tablets in their mouths until the tablets had dissolved. Vitamin C and placebo were kindly provided by Lannacher Heilmittelwerke (Austria).

After 20 minutes of exposure to the waves (the maximum height of the waves was 1 meter), blood samples were taken again to determine the above mentioned parameters. The blood samples were immediately inserted in iced water, then centrifuged at 4 degrees Celsius and stored at −20 degrees Celsius.

To prevent vomiting inside the life raft, the test persons were permitted to signal when they felt seasick. In this case the waves were stopped immediately, the person was helped out of the life raft, and the waves were then re-started. All persons were asked to disembark from the life raft after 20 minutes.

Symptoms were noted on a visual analog scale (0–10 points; 0 indicated no symptoms at all while 10 was indicative of the condition prior to vomiting) immediately after the participants had left the life raft and in half-hour intervals for 3 hours thereafter.

Yawning as well as mild, moderate, or severe nausea/vomiting during the exposure were noted. The 70 volunteers were asked about their sensitivity to seasickness: 22 reported slight sensitivity, 42 moderate, and six strong sensitivity to seasickness.

The entire procedure was repeated the next day, but the active substance was replaced with placebo and vice versa.

At the end of day 2, about three hours after the second exposure, all test persons were asked whether the symptoms of seasickness had been worse on day one or day two.

The primary variable for *statistical analysis* of the effectiveness of vitamin C was the participants' report as to the day on which their symptoms had been worse. This was deemed more reliable than the score on the visual analog scale, and was analyzed using Fisher's test. Appropriate tests were used for secondary variables. Data were calculated using the statistical software Graphpad Prism (version 5.0; GraphPad Software Inc., USA). The level of significance was set to $p < 0.05$. An asterisk (*) indicates that the result was considered significant even after Bonferroni adjustment of the alpha level. The Bonferroni-corrected significance level was set to $p < 0.0025$ for all secondary evaluations.

3. Determination of histamine, diamine oxidase (DAO), tryptase, and vitamin C levels

3.1. Histamine

Histamine levels were determined with a radioimmunoassay (Immunotec, France). Blood was collected in a chilled tube containing EDTA only, and immediately chilled on ice. Samples were centrifuged at 900 g for 10 minutes at 4°C. An acylation buffer and calibrator was added and vortexed immediately. Data were read off from the standard curve by interpolation. The upper normal value was <0.3 ng/ml.

3.2. Diamine oxidase (DAO) (DAO-REA, Sciotec Diagnostics Tulln, Austria)

DAO activity was determined by quantifying the reaction product. Radiolabeled putrescine dihydrochloride was used as substrate. The resulting Δ^1pyrroline containing the radiolabel was extracted selectively from the matrix by a liquid extraction step. A non-toxic chlorine-free solvent with high capacity was used for extraction. Finally, scintillation fluid was added to the organic phase, containing the radiolabeled Δ^1-pyrroline, and radioactivity was determined in a beta counter. The signal is directly proportional to the activity of DAO in the sample.

3.3. Tryptase (Thermo Fisher Scientific, Austria)

Anti-tryptase, covalently bound to a solid phase, reacts with the tryptase in serum. After a washing procedure, enzyme-labeled antibodies to tryptase are added to form a complex. After incubation, unbound enzyme anti-tryptase is washed away and the bound complex is incubated with a developer.

The fluorescence of the eluate is measured after stopping the reaction. Fluorescence is directly proportional to tryptase levels in serum.

3.4. Vitamin C

Vitamin C levels were measured by HPLC (high-pressure liquid chromatography) using the vitamin C measuring kit of Chromsystems®, based on the internal standard according to the manufacturer's recommendations (Vitamin C kit, Chromsystems®, Germany). A BioRad® HPLC device was used (BioRad®, Germany).

Twenty microliters of lithium-heparin plasma were injected with the autosampler into the Chromsystems® HPLC column with pre-column. The flow rate of the mobile phase was 1–1.5 ml/min, isocratic setting, the column temperature was 25°C, and UV detection was performed at 245 nm (BioRad UV detector, model 1706).

4. Results

All 70 volunteers were treated according to protocol on both days.

Seven of these (two women and five men) had no symptoms whatsoever on either day.

4.1. Influence of vitamin C

When asked which of the two days of exposure had been worse, seven of 70 participants (those, who had had no symptoms at all) reported that they had felt the same on both days. All of the remaining 63 participants

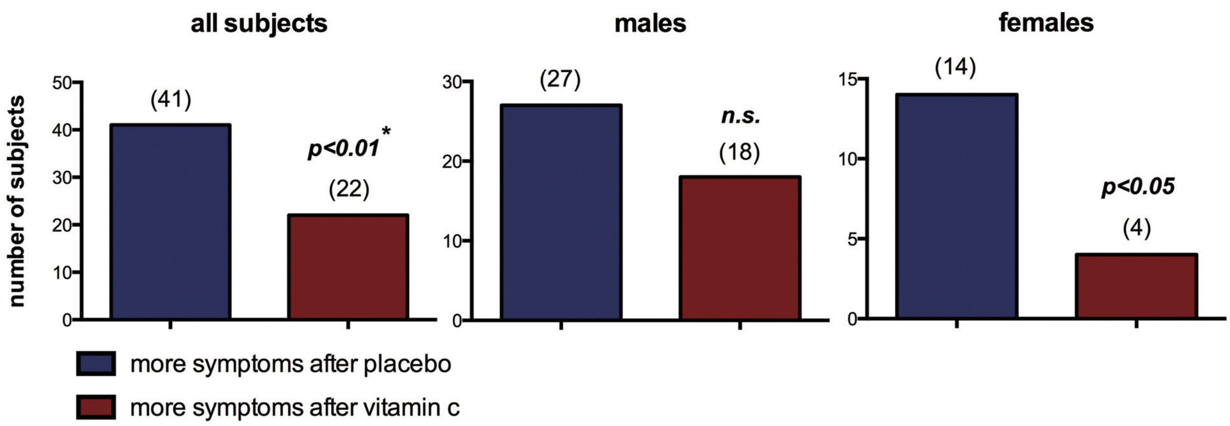

Fig. 1. Symptoms of seasickness after placebo vs. vitamin C in all subjects, and after division by gender.

mentioned the first or the second day.

Altogether, 22/63 participants reported more symptoms after the intake of vitamin C, compared to 41/63 after the intake of placebo. To control for habituation, these data were analyzed in a 2×2 table (Table 1) with the two groups (i.e. the two orders of treatment, VP and PV) in two separate lines ($p = 0.0083^*$; Fisher's test). A significant difference was noted between the two groups in regard of the day of more severe symptoms: group VP felt better on the first day while group PV felt better on the second day. Thus, in each group the majority of participants had less severe and fewer symptoms on the day they had taken vitamin C.

A *gender difference* was noted: women experienced more symptoms with vitamin C in 4/18 cases, and with placebo in 14/18 cases ($p = 0.0498$; Fisher's test). Men had more signs of seasickness with vitamin C in 18/45 cases, and with placebo in 27/45 cases (n.s.) (Fig. 1).

4.1.1. Comparison of age groups younger or older than the median age of 27 years

The median age of all tested persons ($n = 70$) was 27 years. Three persons were 27 years old; the youngest of these was assigned to the "younger" group while the others were assigned to the "older" group.

Test persons (men and women) younger than 27 years of age felt worse with placebo in 21/30 cases, compared to vitamin C in 9/30 cases ($p = 0.0169^*$; Fisher's test).

Test persons (men and women) older than 27 years of age felt better with vitamin C in 20/33 cases, compared to 13/33 cases with placebo (n.s).

4.1.2. Premature termination of exposure

Twenty-three of 63 volunteers 23 persons (11 women and 12 men) wished to leave the life raft at least

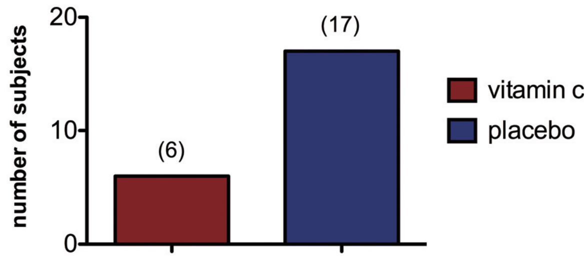

Fig. 2. Number of persons leaving the raft at least once earlier than 20 minutes.

once earlier than the prescribed 20 minutes. Eight of these 23 persons left the life raft earlier on both days (six women and two men). Among those who left the raft before completion of the 20 minutes, persons who took vitamin C had a score of 5.45 on the visual analog scale (range, 0–10) while those who took placebo had a score of 7.57. Of those with a briefer tolerance of exposure in the life raft, 17 had taken placebo and six had taken vitamin C (Fig. 2). In this group, the duration of stay in the life raft was 16.7 ± 4.4 minutes after vitamin C and 13.6 ± 4.7 minutes after placebo ($p = 0.035^*$).

4.1.3. Severity of symptoms during and after exposure

Symptoms experienced during the exposure to waves were yawning, mild nausea, moderate nausea, and severe nausea (sensation prior to vomiting). Differences in *yawning; mild, moderate, and severe nausea* are shown in Fig. 3. The temporal course of severe nausea is shown in Fig. 4.

Women experienced mild nausea more often with placebo ($p = 0.045$), moderate nausea with placebo ($p = 0.007^*$), and severe nausea with placebo ($p = 0.014^*$).

Table 1
Vitamin C was superior to placebo when the test persons rated their symptoms on the two days of testing ($n = 63$)

		Day of more severe symptoms		Total
		Day 1	Day 2	
Sequence of treatment	Day 1: Vitamin C Day 2: Placebo	17	18	35
	Day 1: Placebo Day 2: Vitamin C	23	5	28
Total		40	23	63

$p = 0.0083^*$ (Fisher's test).

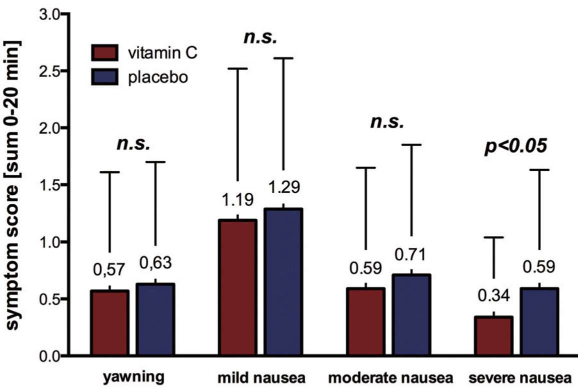

Fig. 3. Symptom scores for yawning; mild, moderate, and severe nausea in relation to the drug taken. Sum of the 5-minute intervals for each symptom during exposure to waves (for the specific symptom: 0 = no; 1 = yes), mean ± SD.

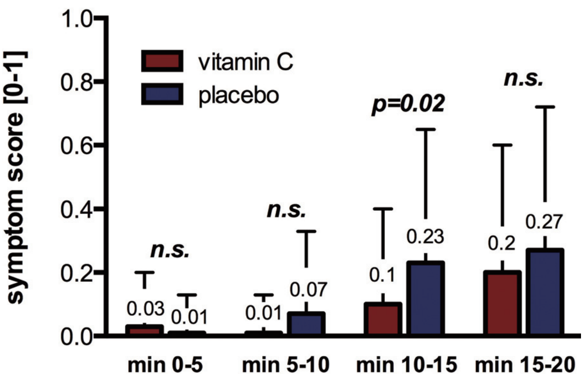

Fig. 4. Symptom score according to time. Mean±SD of the symptom *severe nausea* (0 = no severe nausea; 1 = severe nausea) in 5-minute intervals during exposure to waves.

Persons *younger than 27* years revealed a significant difference in favor of vitamin C ($p = 0.0409$) only in regard of severe nausea. No difference was registered in persons older than 28 years of age.

Comparison of symptoms on the visual analog scale until 180 minutes after completion of the exposure revealed no difference between vitamin C and placebo. However, slightly better results were noted for vitamin C (Table 2). In a repeated measures analysis of variance with three factors (time, treatment, and group),

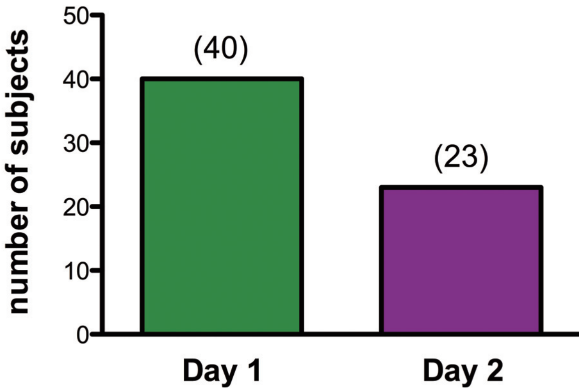

Fig. 5. Day with more severe symptoms. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/VES-140509)

the factor of time was highly significant ($p < 0.001^*$), reflecting the marked reduction of symptoms over a period of three hours. However, the factors of treatment and group were not significant in the three-factor analysis including time, or in separate analyses for each of the five time points.

4.1.4. Comparison of the two days of exposure

The majority of participants reported more severe symptoms on the first day of exposure than the second day: day 1 was rated better by 23/63 persons, and day 2 by 40/63 persons ($p = 0.043$). The procedure used was approximation by normal distribution with continuity correction, not distinguishing between vitamin C and placebo. (Table 1 and Fig. 5).

4.2. Serum parameters

Vitamin C, histamine, and DAO levels before the intake of vitamin C and after exposure to waves are shown in Tables 3–5.

A repeated measures analysis of variance of vitamin C levels, with time and treatment as within-subject factors, showed high significance for both factors (both $p < 0.001^*$). When the two treatments were analyzed separately, a significant increase in vitamin C levels after verum was registered ($p < 0.0001^*$; paired t-test),

Table 2
Symptom scores on the visual analog scale (0–10) after exposure to waves ($n = 70$)

Time point of rating	0 minute	30 minutes	60 minutes	120 minutes	180 minutes
After vitamin C	3.96 ± 3.44	2.04 ± 2.29	0.97 ± 1.82	0.48 ± 1.5	0.45 ± 1.37
After placebo	4.3 ± 3.29	2.06 ± 2.42	1.05 ± 1.85	0.52 ± 1.15	0.29 ± 0.77
	n.s.	n.s.	n.s.	n.s.	n.s.

Table 3
Vitamin C levels before and after exposure to waves following the intake of 2 g of vitamin C or placebo ($n = 70$; normal range of vitamin C: 4.6–14.9 mg/l)

Vitamin C levels	Before intake	After exposure	Significance (paired t-test)
Vitamin C	12.98 ± 4.57 mg/l	26.03 ± 6.94 mg/l	$p < 0.0001^*$
Placebo	14.48 ± 3.88 mg/l	13.99 ± 3.56 mg/l	n.s.

Table 4
Histamine levels before and after exposure to waves following the intake of 2 g of vitamin C or placebo ($n = 70$; normal histamine level $<$ 0.3 ng/ml)

Histamine levels	Before intake	After exposure	Significance (paired t-test)
Vitamin C	0.17 ± 0.1 ng/ml	0.21 ± 0.1 ng/ml	$p = 0.003^*$
Placebo	0.25 ± 0.45 ng/ml	0.35 ± 0.82 ng/ml	n.s.

Table 5
DAO levels before and after exposure to waves following the intake of 2 g of vitamin C or placebo ($n = 70$; normal DAO level: > 10 U/ml)

DAO levels	Before intake	After exposure	Significance (paired t-test)
Vitamin C	16.98 ± 11.37 U/ml	20.39 ± 13.86 U/ml	$p < 0.001^*$
Placebo	16.89 ± 12.45 U/ml	18.42 ± 13.46 U/ml	n.s.

whereas vitamin C levels after placebo remained unchanged (Table 3).

Histamine levels increased in 79/135 samples, remained the same in 20/135, and decreased in 36/135. A repeated measures analysis of variance of histamine levels revealed no significance for either factor. A separate analysis of each treatment showed a significant increase in histamine levels after the intake of vitamin C and exposure ($p = 0.003$; paired t-test), but not after the intake of placebo (Table 4).

A repeated measures analysis of variance of DAO levels revealed the significant impact of time ($p < 0.001^*$), but not treatment. When the two treatments were analyzed separately, DAO levels were found to be significantly increased ($p < 0.001^*$; paired t-test) after vitamin C and slightly increased after placebo (n.s.) (Table 5).

Two persons who had elevated *tryptase* levels (12.4 μg/l and 14.9 μg/l) prior to the test experienced severe symptoms.

5. Discussion

The prime outcome of the investigation was that vitamin C helps to suppress the symptoms of seasickness. A gender difference was noted: women (who are generally more prone to motion sickness) and men younger than 27 years of age benefited to a greater extent from the intake of vitamin C. Older persons, who are usually less sensitive, did not experience such benefits. The same results in regard of gender and age were noted by Bos et al. [4]. The difference on the visual analog scale was in favor of vitamin C (the mean score for vitamin C was 3.9, versus 4.3 for placebo), but not significant. Significantly more persons who had undergone placebo treatment left the raft earlier than 20 minutes.

The second day of exposure to waves was rated the better one, which confirms the fact that habituation occurs over time. The percentage of persons who felt better with placebo was 21.7% (5/23) on day one and 42.5% (17/40) on day two. Placebo rates were usually between 20% and 30%. The rather low placebo rate on day one indicates that the test procedure was strenuous. On training, marine cadets spend just 5 minutes in a life raft. The relatively high rate of well-being with placebo on day two is indicative of habituation.

The majority of persons have elevated histamine levels in blood when being exposed to waves. An increase was observed in both groups, but was not significant in the placebo group. This appears to be due to the much greater variation of results compared to the vitamin C group (Table 4). The reason for the greater variation is unclear. Taken together, both groups revealed a significant increase ($p < 0.001$). For obvious reasons, histamine levels cannot be measured in the brain. Potential changes in histamine levels at this location remain speculative in nature. In animal studies, the blockage of histidine decarboxylase showed histamine to be the most important cause of seasickness [14].

An increase in DAO levels was registered in both groups, but was more significant in the vitamin C group after oral intake of 4×500 mg of vitamin C. This fact may be of interest in the treatment of histamine-intolerant persons, who frequently experience motion sickness.

No change was registered in tryptase levels throughout the period of investigation. Two participants had elevated tryptase levels prior to exposure (12.4 μg/l and 14.9 μg/l, respectively) and suffered severe symptoms.

Patients with mastocytosis and elevated tryptase levels may release histamine spontaneously or under stress. Some of these patients experience nausea, which can be suppressed by daily intake of vitamin C (1–2 g).

The uptake of vitamin C is rather slow when swallowed, and the substance is excreted rather rapidly. As humans are unable to synthesize vitamin C (in contrast to rats), regular intake of the substance is mandatory. Blood levels of vitamin C increase more rapidly when the tablets are dissolved in the mouth than when swallowed. Therefore, the success of treatment is greatly dependent on raising vitamin C levels rapidly by dissolution in the mouth.

Inhabitants of the Samoa islands ingest one or two mangoes before they go to sea [13]. Mangoes contain almost as much vitamin C as lemons relative to weight [20].

The Chinese are more sensitive to seasickness than Caucasians [10]. This has been attributed to allelic variation in the alpha 2A-adrenergic receptor in the former population [14].

Two theories have been postulated as an explanation for seasickness: the classical sensory mismatch theory and the subjective vertical conflict model. Both are based on the thesis that seasickness occurs when the anticipated motion does not coincide with the actual motion [2].

Even fish are known to experience seasickness. The dominance of the vestibular system over the ocular system was proven in a goldfish model [12]. Blind persons are prone to seasickness, whereas persons with a defect in the vestibular system are not [5].

5.1. Motion sickness is not only a problem at sea

Persons (especially children) sitting in the second row of a car, the rear portion of a bus, or with no vista on a ship [4] are prone to motion sickness. The latter is also a major problem in high-speed trains, helicopters [6], and in space medicine [5,11]. Seasickness was located as the cause of two recent accidents with sailing yachts in the Mediterranean Sea, leading to death and the loss of ships. An important factor of survival is the degree of hypothermia, which is exaggerated by seasickness [18,19]. Therefore, the fact that severe seasickness causes persons to contemplate or even attempt suicide is by no means unusual.

None of the drugs recommended for seasickness alleviate the condition in all cases. We found vitamin C to be effective in suppressing the symptoms of seasickness in women and men younger than 27 years of age, and therefore recommend the intake of vitamin C tablets in persons experiencing the onset of seasickness.

In contrast to other drugs which have to be taken several hours before exposure to waves, vitamin C may be taken at short notice and is entirely devoid of side effects. It does not cause dizziness as antihistamines do and does not influence eyesight as scopolamine does.

Histamine levels are increased during exposure to waves. DAO levels are increased by the intake of vitamin C. The fact that both of our groups fared better on the second day of exposure to waves is indicative of habituation over time. Based on the present investigation, nausea and its treatment are currently being addressed as a potential problem for sailors at sea in the German Navy.

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Conflict of interest

The authors declare no conflict of interest.

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